

What is Claimed is:

1. A method for first line treatment of type 2 diabetes, in a drug naive human patient, which comprises administering to a drug naive human patient in need of treatment, as first line therapy, a low dose of a combination of metformin and glyburide.
2. The method as defined in Claim 1 wherein the daily dosage of metformin administered is less than 800 mg.
3. The method as defined in Claim 1 wherein the low dose combination of metformin and glyburide provides at least substantially equivalent efficacy in treating diabetes in drug naive patients, but with substantially reduced side effects, as do combinations of metformin and said glyburide employed in substantially higher daily dosages as prescribed in generally accepted medical practice for first line therapy in treating diabetes.
4. The method as defined in Claim 1 wherein the starting daily dosage of metformin is as low as about one-fifth of the starting daily dosage of metformin employed in generally accepted medical practice for first line therapy for treating diabetes.
5. The method as defined in Claim 4 wherein the daily maintenance dosage of metformin employed is up to that employed in generally accepted medical practice for first line or second line therapy for treating diabetes.
6. The method as defined in Claim 1 wherein the starting daily dosage of glyburide is as low as about one-fifth of the starting daily dosage of glyburide employed in generally accepted medical practice for first line therapy for treating diabetes.

7. The method as defined in Claim 6 wherein the daily maintenance dosage of glyburide employed is up to that employed in generally accepted medical practice for first line therapy or second line therapy for treating  
5 diabetes.

8. The method as defined in Claim 1 wherein the metformin is administered in a daily dosage in an amount within the range from about 160 mg to about 750 mg, and  
10 the glyburide is administered in a daily dosage in an amount within the range from about 0.5 to about 15 mg.

9. The method as defined in Claim 1 wherein the low dose combination of metformin and glyburide is  
15 formulated as a single dosage form.

10. The method as defined in Claim 1 wherein the metformin is employed in a weight ratio to glyburide within the range from about 400:1 to about 50:1.  
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11. The method as defined in Claim 1 wherein the metformin and glyburide are employed in a weight ratio to each other of about 200:1 or 100:1.

12. The method as defined in Claim 1 wherein the metformin is administered in an amount within the range from about 125 to about 750 mg, one to four times daily, provided that the maximum daily dosage for metformin is about 750 mg per day, but more than about 225 mg, and the  
25 glyburide is administered in an amount within the range from about 0.75 to about 5 mg, one to four times daily, up to a maximum of 15 mg per day.  
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13. The method as defined in Claim 1 wherein the metformin is administered in an amount within the range  
35 from about 250 to about 500 mg, and the glyburide is

administered in an amount within the range from about 1.25 to about 5 mg.

14. The method as defined in Claim 1 wherein the metformin/glyburide combination contains of 250 mg metformin/1.25 mg glyburide.

15. The method as defined in Claim 1 wherein the metformin/glyburide combination contains 500 mg metformin/2.5 mg glyburide.

16. The method as defined in Claim 1 wherein the metformin/glyburide combination contains 500 mg metformin/5 mg glyburide.

17. The method as defined in Claim 1 wherein a metformin/glyburide 250/ mg/1.25 mg dosage is administered once a day or twice a day.

18. The method as defined in Claim 19 wherein the metformin/glyburide 250 mg/1.25 mg dosage is administered to patients with a baseline HbA<sub>1c</sub> > 9% or a fasting glucose > 200 mg/dL twice daily, with dosage increases, where necessary, in increments of 250 mg/1.25 mg every 2 weeks, up to the minimum effective daily dose necessary to achieve adequate glycemic control.

19. The method as defined in Claim 1 wherein said metformin is employed in a daily dose as employed in generally accepted medical practice for first line therapy or second line therapy for treating diabetes.

20. The method as defined in Claim 1 wherein glyburide is employed in a daily dose as employed in generally accepted medical practice for first line therapy or second line therapy for treating diabetes.

21. The method as defined in Claim 1 wherein the low dose combination comprising 250 mg metformin and 1.25 mg glyburide characterized in that it has at least substantially equivalent efficacy to a formulation comprising 500 mg metformin and 2.5 mg glyburide in treating diabetes with respect to decrease in hemoglobin A<sub>1c</sub>, decrease in insulin resistance, increase in post-prandial insulin levels and/or decrease in post-prandial glucose excursion, while providing substantially reduced incidence of adverse side effects which are hypoglycemia and gastrointestinal side effects.

22. A method for first line treatment of type 2 diabetes, in a drug naive human patient, which comprises administering to a drug naive human patient in need of treatment, as first line therapy, a low dose of a combination of metformin and glyburide wherein the starting daily dosage is 250 mg metformin and 1.25 mg glyburide.

23. A method for first line treatment of type 2 diabetes, in a drug naive human patient, which comprises administering to a drug naive human patient in need of treatment, as first line therapy, a therapeutically effective low dose of a combination of metformin and glyburide wherein the starting daily dosage is 250 mg metformin and 1.25 mg glyburide twice a day or 500 mg metformin and 2.5 mg glyburide once a day.

24. A method for first line treatment of type 2 diabetes, in a drug naive human patient, which comprises administering to a drug naive human patient in need of treatment, as first line therapy, a therapeutically effective low dose of a combination of metformin and glyburide wherein the starting daily dosage is 500 mg metformin and 5 mg glyburide.

25. A method for first line treatment of type 2 diabetes, in a drug naive human patient, which comprises administering to a drug naive human patient in need of treatment, as first line therapy, a therapeutically effective low dose of a combination of metformin and glyburide wherein the glyburide is such that the glyburide bioavailability is comparable to the glyburide bioavailability obtained with a separate administration of metformin and glyburide.

26. The method as defined in Claim 25 where in the combination of metformin and glyburide the particle size distribution of the glyburide is such that at most 10% of the particles are less than 2  $\mu\text{m}$  and at most 10% of the particles are greater than 60  $\mu\text{m}$ .

27. The method as defined in Claim 25 wherein the glyburide has a particle size distribution such that at most 10% are less than 3  $\mu\text{m}$  and at most 10% are greater than 40  $\mu\text{m}$ .

28. The method as defined in Claim 25 wherein the glyburide has a particle size distribution such that at most 25% are less than 11  $\mu\text{m}$  and at most 25% are greater than 46  $\mu\text{m}$ .

29. The method as defined in Claim 25 wherein 50% of the glyburide patients are less than 23  $\mu\text{m}$ .

30. The method as defined in Claim 25 wherein the glyburide has a particle size distribution of about 25% undersize value not more than 6  $\mu\text{m}$ , about 50% undersize value 7 to 10  $\mu\text{m}$  and about 75% undersize value not more than 23  $\mu\text{m}$ .

31. The method as defined in Claim 25 wherein the starting daily dosage is 250 mg metformin/1.25 mg glyburide or 500 mg metformin/2.5 mg glyburide.

5 32. The method as defined in Claim 3 wherein the substantially reduced side effects are hypoglycemia and/or gastrointestinal side effects which are diarrhea, nausea/vomiting and/or abdominal pain.

10 33. The method as defined in Claim 32 wherein the incidence of hypoglycemia in drug naive patients resulting from use of the low dose metformin-glyburide combination is 1/3 or less than in patients treated with double the metformin-glyburide present in the low dose  
15 metformin-glyburide.

20 34. The method as defined in Claim 32 wherein the incidence of gastrointestinal side effects in drug naive patients resulting from use of the low dose metformin-glyburide combination is 20% less than in patients treated with twice the amount of each of the metformin-glyburide present in the low dose metformin-glyburide.

25 35. A method for lowering blood glucose in a hyperglycemic human patient, which comprises administering to a drug naive human patient in need of treatment, as first line therapy, a therapeutically effective amount of a low dose pharmaceutical formulation as defined in Claim 1.

30 36. A method for decreasing insulin resistance and/or decreasing hemoglobinA<sub>1c</sub> and/or increasing post-prandial insulin levels and/or decreasing post-prandial glucose excursion, in a human patient, which comprises  
35 administering to a drug naive human patient in need of treatment as first line therapy a pharmaceutical formulation as defined in Claim 1.